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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

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02/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/578,900	CARULLI ET AL.	
	Examiner	Art Unit	
	J. E. Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,7,48-51,53-60 and 62-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,7,48-51,53-60 and 62-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :6/27/2007, 8/9/2006, 7/14/2004, 10/10/2000.

DETAILED ACTION

This Action is in response to the communication filed on 10/4/2007.

The amendment filed 10/4/2007 is acknowledged and has been entered.

Claims 1, 2, 6, 7, 48-51, 53-60, 62-67 are currently pending in the application and are addressed herein.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Information Disclosure Statement

Attached are copies of the initialed Information Disclosure Statements (IDS) submitted 6/27/2007, 8/9/2006, 7/14/2004 and 10/10/2000, as requested. Applicant also requested a copy of the IDS submitted 6/8/2001; however, no IDS for this date appears in the electronic file. In fact no submission of any kind is found for 6/8/2001. Applicants are asked to review their records and submit a copy of the IDS with a copy of the return receipt for this IDS so that it may be reviewed by the Examiner.

Claim Rejections - 35 USC § 101 and 112, 1st paragraph combined

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, 7, 48-51, 53-60, 62-67 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility.

The instant claims are drawn to a method for identifying a reagent that decreases the amount of a lipid comprising the steps of exposing the reagent to a nucleic acid comprising SEQ ID NO; 1 or 2 or to a polypeptide comprising SEQ ID NO: 3 or 4, determining whether said reagent binds to said nucleic acid or said polypeptide, administering said reagent that binds to said nucleic acid or said polypeptide to an animal or a cell and determining whether said reagent decreases the amount of said lipid in said animal or said cell (claim 1); and, a method for identifying a reagent that decreases the amount of a lipid comprising the steps of identifying and agent that binds to a nucleic acid comprising SEQ ID NO: 1 or 2, measuring the binding of the first molecule to SEQ ID NO: 1 or 2, and administering said molecule that binds to SEQ ID NO: 1 or 2 to a cell and determining whether said molecule decreases the amount of said lipid in said cell (claim 6)

When considering the utility of the instant claims, the issue is not merely whether Zmax1 and HBM have utility in and of themselves, but whether the claimed methods of identifying molecules that reduce a lipid have utility under 35 U.S.C. § 101. To be clear, the issue is whether or not methods of identifying a reagent that binds to HBM or Zmax1 nucleic acid or

polypeptide and further determining if this reagent reduces a lipid has credible, substantial and specific or well-established utility.

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification. The specification clearly asserts that the claimed methods have utility for identifying molecules involved in lipid regulation. The specification, as well as the prior art indicate, indicates that lipids are involved in many different biological processes. Furthermore, it is recognized that an aberrant serum lipid levels is associated with disease. For instance, aberrantly high levels of serum lipids has been associated with atherosclerosis and other various diseases. Since identifying molecules associated with disease is credible, the asserted utility for the claims is credible.

The second issue is whether substantial and specific utilities are disclosed in the specification. As indicated above, the specification must assert substantial AND specific utility for the claimed methods. With respect to "specific" utility, MPEP 2107.01 states,

A "specific utility" is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. Office personnel should distinguish between situations where an applicant has disclosed a specific use for or application of the invention and situations where the applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful. For example, indicating that a compound may be useful in treating unspecified disorders, or that the compound has "useful biological" properties, would not be sufficient to define a specific utility for the compound. Similarly, a claim to a polynucleotide whose use is disclosed simply as a "gene

probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed. Contrast the situation where an applicant discloses a specific biological activity and reasonably correlates that activity to a disease condition. Assertions falling within the latter category are sufficient to identify a specific utility for the invention. Assertions that fall in the former category are insufficient to define a specific utility for the invention, especially if the assertion takes the form of a general statement that makes it clear that a "useful" invention may arise from what has been disclosed by the applicant. Knapp v. Anderson, 477 F.2d 588, 177 USPQ 688 (CCPA 1973).

The regulation of serum lipid levels is recognized in the art as a very complex process that involves not one single factor, but many different factors including diet as well as the function of many different genes. For instance, Ye et al. (Am. J. Clin. Nutr. 2000; Vol. 72 (Suppl), pages 1275S-1284S; previously cited) teaches that genes influence quantitative variations in plasma lipoprotein concentrations (see abstract). Specifically, Ye reviews a number of DNA sequence polymorphisms (specifically, polymorphisms in the genes encoding ApoA-I, ApoA-IV, ApoB, ApoC-III, ApoE, LPL, CETP, LCAT, and LDL receptor) which are thought to be involved in plasma lipid regulation. Therefore, Ye teaches that regulating serum lipid levels is a complex process that involves many different biological and biochemical factors and processes including diet as well as the activity of at least 9 specific gene products.

Therefore, it is clear that “lipid regulation” is not limited to a single process but encompasses the involvement of many different biological and biochemical factors and

processes. As such, the assertion that the method has utility for identifying molecules involved in lipid regulation is not a specific utility.

It is acknowledged that the specification asserts that Zmax1 and HBM are members of the LDL receptor family, based on sequence similarity alone. The specification also asserts that HBM and Zmax1 are "involved in lipid regulation". However, the specification does not disclose how Zmax1 and HBM are specifically involved in lipid regulation.

Furthermore, the claimed methods do not have a specific utility because the HBM and Zmax1 molecules used in the instant methods could be substituted with any molecule and the method could still be used to identify molecules that reduce lipids. That is, the instant claims are not specific because the methods could be practiced using any molecule, not just HMB or Zmax1.

With respect to "substantial" utility, MPEP 2107.01 states:

A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":…

(C) A method of assaying for or identifying a material that itself has no specific and/or substantial utility;

In the instant case, the claimed invention is not considered a substantial utility because additional experimentation would be required in order to determine that the identified molecules which bind to HBM or Zmax1, as well as HBM and Zmax1 themselves, are actually involved in reducing a lipid.

The last consideration is whether there is a well-established utility for the claimed invention. The specification and relevant art do not appear to disclose any "well-established" established utilities for the claimed method of identifying molecules involved in reducing a lipid using Zmax1 and HBM.

Regarding the involvement of HBM in lipid regulation, the specification discloses that biochemical tests were performed to measure the serum levels of various lipid containing molecules and precursors in affected and unaffected HBM family members to test whether HBM affects lipid regulation (see Example 3, starting at p. 125). The specification discloses that HDL levels are "generally higher in affected males than unaffected males" (see p. 126, line 21-27).

Regarding Zmax1's involvement in lipid regulation, there does not appear to be any data presented indicating any particular lipid profile with Zmax1. The basis of Zmax1 involvement in lipid regulation appears to be based on the sequence similarity of Zmax1 with LDL-receptors and its similarity to HBM.

However, neither the specification nor the art of record teaches how HBM and Zmax1 are specifically involved in lipid regulation. Therefore, at best, Applicants have identified an association between a specific polymorphism (HBM) and a specific lipid profile without disclosing how HBM, let alone Zmax1, is involved in determining lipid levels. Since the function of HBM and Zmax1 has not been identified, further experimentation would be necessary in order to determine how HBM and Zmax1 are involved in lipid regulation before the claimed methods can be considered specific and substantial.

In conclusion, the claimed invention must be supported by a specific and substantial asserted utility or a well-established utility. The claimed invention is drawn to method of identifying reagents that reduce a lipid wherein the methods rely on identifying molecules which bind to HBM or Zmax1 sequences.

Claims 1, 2, 6, 7, 48-60 and 61-67 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, 7, 48-51, 53-60, 62-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method for identifying a reagent that decreases the amount of a lipid by first identifying molecules that bind to Zmax1 or HBM polynucleotide (SEQ ID NO: 1 and 2) or polypeptide (SEQ ID NO: 3 and 4) and then administering the reagent to an animal or a cell and determining if the reagent decreases the amount of lipid in the animal or cell.

The unpredictability of the art and the state of the prior art

The art of record clearly indicates regulating the level of a lipid (e.g., increasing or decreasing lipid levels) is a complex process that involves the action of many different genes as well as other factors such as diet. Specifically, Ye et al. (Am. J. Clin. Nutr. 2000; Vol. 72

(Suppl), pages 1275S-1284S; previously cited) teaches that genes influence quantitative variations in plasma lipoprotein concentrations (see abstract). Specifically, with respect to plasma lipid levels, Ye reviews a number of DNA sequence polymorphisms (specifically, polymorphisms in the genes encoding ApoA-I, ApoA-IV, ApoB, ApoC-III, ApoE, LPL, CETP, LCAT, and LDL receptor) which are thought to be involved in plasma lipid regulation. Therefore, Ye teaches that regulating serum lipid levels is a complex process that involves many different biological and biochemical factors and processes including diet as well as the activity of at least 9 specific gene products.

Therefore, it is clear that regulating the amount of a lipid in an animal or cell is not limited to a single process but encompasses the involvement of many different biological and biochemical factors and processes.

Additionally, in order for the method to be able to identify molecules involved decreasing the amount of a lipid, it is imperative that HBM and Zmax1 are specifically involved lipid regulation. The specification discloses that HBM and Zmax1 are LDL-receptor family members, based on sequences similarity to known LDL-receptors as well as the association of the HBM polymorphism with a particular lipid profile. There is no disclosure in the specification or prior art which indicates that either HBM or Zmax1 is a functional LDL receptor that is directly involved in lipid regulation.

Furthermore, the relevant art at the time of filing recognized that LDL-receptors could be involved in functions other than lipid regulation. For instance, Willnow et al. (Nature Cell Biol.; Vol. 1, October 1999, pages E157-E162) teaches,

> "Lipoprotein receptors used to be viewed simply as the means by which cells were supplied with lipids for energy production and membrane synthesis. This perception has

> now changed dramatically. Megalin, a member of the low density lipoprotein receptor gene family, turns out to mediate the endocytic uptake of retinoids and steroids, thus helping to regulate their biological function. Other members of this receptor family interact with cytosolic signaling proteins, giving this evolutionary ancient family of receptors and entirely unexpected new role as transducers of extracellular signals." (See abstract, emphasis added).

Therefore, the prior art teaches that LDL-receptors (which appellants assert includes Zmax1 and HBM) can be involved in processes other than lipid regulation, such as endocytic uptake of retinoids and steroids. Since the LDL receptor is known to be involved in processes other than lipid metabolism, one of ordinary skill in the art would not be able to associate Zmax1 with LDL regulation based on sequence similarity alone.

Finally, the art also teaches that gene association studies are typically wrong. For instance, Lucenti (The Sceintist, 2004; Vol. 18(24), page 20) teaches:

> "The first published study linking gene to disease is often far from the last word on the subject… Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one third chance that studies will reliably confirm the finding."

Therefore, the mere association of HBM with a particular profile does not conclusively indicate that HBM or Zmax1 cause that specific lipid profile nor does it indicate how they specifically affect the lipid profile. Therefore, further experimentation is necessary.

In view of the totality of the prior art, it is clear that a mere observation that HBM may be associated with a particular lipid profile and that HBM and Zmax1 may be members of the LDL receptor family of proteins, is not sufficient to establish that HBM and Zmax1 are directly involved in lipid regulation, which is required in order for the claimed methods to have to be enabled.

Working Examples and Guidance in the Specification

The specification asserts that Zmax1 and HBM are LDL-receptor family members involved in lipid regulation. The specification asserts that Zmax1 is involved in lipid regulation based on alignments alone. The specification also asserts that HBM is involved in lipid regulation based on sequence similarity as well as the association of the HBM polymorphism with a particular lipid profile. For example, Example 3 in the specification discloses,

> "Since Zmaxl has similarity to the LDL receptor family of genes, it may be involved in lipid metabolism. However, others have reported that lipid profile variables did not show significant association with bone mass and could not be used as indicators for bone mineral density (Zabaglia et a1., "An exploratory study of association between lipid profile and bone mineral density in menopausal women in a Campinas reference hospital," Cad. Saude Publica 14: 779-86 (1998)). (Emphasis added)

> "To test whether the HBM gene was involved in lipid regulation, biochemical tests were performed to measure serum level of various lipid containing molecules or precursors in affected and unaffected HBM family members to test whether the HBM mutation in the Zmaxl gene effects lipid metabolism… The results obtained were statistically significant: (1) Triglyceride levels were generally lower in affected individuals than in unaffected individuals, and (2) very low density lipoprotein (VLDL) levels were generally lower in affected individuals than in unaffected individuals. Additionally, the following comparisons approached statistical significance (p=0.06): (1) high density lipoprotein (HDL) levels were higher in affected males than in unaffected males, and (2) the ratio of low density lipoprotein (LDL) to high density lipoprotein (HDL) was generally higher in affected males than in unaffected males." (See p. 126, lines 4-27).

Here, Applicants indicate the Zmax1 has "similarity" to the LDL receptor family of genes, but it is not clear exactly how similar Zmax1 is to the LDL receptors. Applicants acknowledge that the prior art had not made a connection between lipid metabolism and bone mineral density. In this Example, Applicants attempt to associate the HBM gene with lipid metabolism by evaluating the serum levels of some lipid containing molecules in individuals with and without HBM. The only statistically significant data disclosed indicates the individuals having the HBM

polymorphism also have generally lower triglycerides levels and generally lower VLDL levels compared to individuals without HBM.

In contrast to the above disclosure, Zabaglia (1998, previously cited) teaches that HDL levels showed an inverse correlation to bone mass in postmenopausal women to a very high degree of statistical significance, indicating that as bone mass increases HDL decreases (while the specification indicates males having high bone mass had increased HDL levels). The only apparent differences between to two data sets is that the specification was analyzing HDL levels in men with high bone mass and Zabaglia was analyzing 1HDL levels in postmenopausic woman. It is not clear why the association of HBM with HDL is not consistent between the two groups, bringing into question association of HBM with lipid regulation.

The specification does not provide any working examples wherein the claimed method was used to positively identify a molecule involved in lipid regulation.

Quantity of Experimentation

Additional experimentation would be required in order to first establish that HBM and Zmax1 are involved in lipid regulation. This would additional experimentation to identify which biochemical process/processes of lipid regulation HBM and Zmax1 are involved in as well as identify how Zmax1 and HBM were specifically "involved" in lipid regulation. Once these molecules were identified, additional further experimentation would be required in order to determine which of the molecules actually caused HBM or Zmax1 to reduce the lipid levels in the animal or cell.

Level of the skill in the art

The level of the skill in the art required to practice the claimed method is deemed to be high.

Conclusion

Considering the nature of the invention, the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the limited amount of working examples and guidance provided, and the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure for the instant claims. Therefore, additional experimentation is required before one of skill in the art could make and use the claimed invention as indicated. The amount of additional experimentation required to perform the broadly claimed invention is undue.

Response to Arguments

Applicant's arguments filed 6/27/2007 have been fully considered but they are not persuasive to overcome the pending utility and enablement rejections.

Applicants argue that the claimed invention has a specific utility based on the assertion that HBM and Zmax1 are involved in lipid regulation. Applicants assert the instant case is analogous to the facts of *In re Brana* where chemical compounds for treating cancer were determined to have utility. Applicants contend that cancer is complex and, like lipids, can involve many pathways.

In response, involvement in lipid regulation is not considered a specific utility. Cancer, although it may be complex and may involve many pathways is a specific disease. Lipids are a

class of molecules that encompass all fat soluble, naturally occurring molecules (a vast number of different molecules). Examples of lipid molecules includes fats, oils, waxes, cholesterol, sterols, fat-soluble vitamins (such as vitamins A, D, E and K), monoglycerides, diglycerides, phospholipids, and others. Therefore, being "involved in lipid regulation" does not constitute a specific utility.

Applicants assert that a disclosure that identifies a particular biological activity of a compound and explains how that activity can be utilized in a therapeutic application provides a specific activity.

The Office acknowledges that a disclosure that identifies a particular biological activity of a compound and explains how that activity can be utilized in a therapeutic application provides a specific activity. However, in this case, a particular biological activity of the Zax1 and HBM compounds has not been disclosed because merely being involved in the regulation of any lipid is not a particular biological activity. Furthermore, there does not appear to be an explanation of how the activity can be used in a therapeutic application.

Applicants argue that the specification provides evidence that Zmax1 (LRP5) is a member of the LDL receptor family. Applicants also refer to a figure 3 from Brown et al. which shows LRP5 as a member of the LDL receptor family.

In response, being an LDL receptor family member does not confer a specific utility because it is taught that LDL receptors can be involved in functions other than lipid regulation (e.g., see Willnow, above).

Applicants argue that the fact the LDL receptors were known were known to be involved in functions other than lipid regulation is not dispositive of the asserted utility. Applicants assert that they have showed an altered lipid profile and ApoE binding to Zmax1.

In response, it is the Office's position that considering all of the evidence of record including the teaching of Ye and Zabaglia, it is not more likely than not one of skill in the art would believe the truthfulness of the asserted utility. It is noted that there does not appear to be any disclosure of an altered lipid profile for Zmax1.

With respect to the assertion that they have failed to show that Zmax1 or HBM is directly involved in lipid regulation, Applicants contend that direct or indirect involvement is sufficient.

In response, it is respectfully noted that the utility rejection indicates that the specification does not disclose how Zmax1 and HBM are specifically involved in lipid regulation. It is acknowledged that direct involvement is not a requirement. However, the evidence of which has been presented is that HBM and Zmax1 are members of the LDL receptor family and that the HBM polymorphism appears to correlate with altered lipid profile. However, the art teaches that LDL receptors can be involved in many different types of function including functions other than lipid regulation. Furthermore, evidence has been presented that casts doubt on the correlation of bone mass to lipid levels. Finally, the asserted utility is that the claimed method can identify reagents that are involved in lipid regulation; however, this is not considered a specific utility because lipids encompass a vast number of different molecules.

Applicants argue that the claims turn on screening reagent that bind to HBM/Zmax1 and further decrease a lipid, therefore, HBM/Zmax1 could not be substituted with another molecule.

In response, to be clear, the Examiner was only pointing out that if HBM/Zmax1 were substituted with another molecule in the claimed methods, the result of the methods would still be the identification of a reagent that decreases the amount of a lipid in a cell or animal. It is acknowledged that substituted method would not identify a reagent that binds to HBM/Zmax1.

Applicants assert that reliance on Knapp v. Anderson is misplaced.

In response, it is noted that the quoted of Knapp v. Anderson comes directly from MPEP 2107.01 General Principles Governing Utility Rejections (see under subsection I. A. specific utility). Therefore, the reliance on Knapp v. Anderson is not misplaced.

Applicants argue that the claimed method meets the substantial utility requirement as no additional experimentation of HBM/Zmax1 involvement in lipid regulation is required because one of skill in the art would not have doubted the asserted utility.

In response, based on the evidence as a whole, additional experimentation would have been required in order to determine HBM/Zmax1 involvement in lipid regulation.

With respect to the enablement rejection, Applicants point out that the candidate reagents screened must bind to a Zmaxl or HBM polypeptide or nucleic acid, therefore, it would appear the claims require a "direct action."

In response, it is acknowledged that the claims require a “direct action”, the binding of the reagent to the HBM or Zmax1 molecule.

Applicants take issue with the assertion that there is no indication of a direct involvement in lipid regulation. Applicants argue that there is no statutory requirement that involvement be

"direct" for the purpose of claiming a screening assay. Applicants contend that no further experimentation is necessary to make and use the claimed invention. It is asserted that the Office appears to support its argument on the requirement that to be patentable, one must explain "how" something operates, but screening assays have been used for a long time, wherein full elucidation of the scientific principle was not known or needed for the purposes of the screen. Applicants argue that in fact, how or why an invention works is not required for patentability.

In response, it is acknowledged that there is no statutory requirement that involvement be "direct" for the purpose of claiming a screening assay. The rejection merely points out that there is no "direct" evidence of HBM/Zmax1 involvement in lipid regulation. With respect to the evidence provided in the specification, which appears to be indirect evidence, the prior art of record (e.g., Ye, Willnow, Lucenti) supports the notion that further experimentation would be required.

Therefore, Applicants arguments are not persuasive.

Conclusion

2. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner, Art Unit 1635